(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 November 2001 (22.11.2001)

PCT

(10) International Publication Number
WO 01/87276 A1

(51) International Patent Classification[7]: A61K 9/70, A61F 13/02, A61L 15/16, A61M 37/00

(21) International Application Number: PCT/KR01/00783

(22) International Filing Date: 15 May 2001 (15.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000-26091 16 May 2000 (16.05.2000) KR

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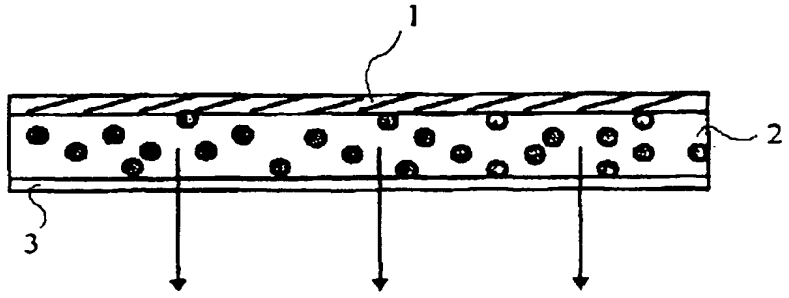
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HYDROGEL COMPOSITION FOR TRANSDERMAL DRUG DELIVERY



(57) Abstract: The present invention relates to a hydrogel composition for transdermal drug delivery, more specifically to a hydrogel composition for transdermal drug delivery containing acrylate polymers like acrylic acid polymer, methacrylic acid polymer, alkyl acrylate polymer, alkyl methacrylate polymer or copolymers thereof as compatibilizers which enable both hydrophilic and lipophilic permeation enhancers to be applicable in the hydrogel composition in order to effectively control skin penetration of drugs.

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HYDROGEL COMPOSITION FOR TRANSDERMAL DRUG DELIVERY

FIELD OF THE INVENTION

The present invention relates to a hydrogel composition for transdermal drug delivery and more specifically, to a hydrogel composition for transdermal drug delivery comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an acrylate polymer which compatibilizes the lipophilic component, i.e. the enhancer, with the hydrophilic polymer base and which renders a uniform composition which is thermodynamically stable. The acrylate polymers such as acrylic acid polymers, methacrylic acid polymers, alkyl acrylate polymers, alkyl methacrylate polymers or copolymers thereof function as compatibilizers in this invention which enables both the hydrophilic and lipophilic components to be uniformly mixed in a hydrogel composition thereby providing for effective drug delivery.

BACKGROUND OF THE INVENTION

Transdermal drug delivery has many advantages over oral or injection means for administering drugs into the body such as efficiency and easiness of control of drug release and administration. Transdermal delivery of various drugs is well known in the art of drug delivery. However, not all drugs can be applied as a transdermal drug delivery system because most of the drugs cannot effectively penetrate the skin. Therefore, the skin-penetration of drugs has to be increased by altering the physical and chemical properties of the skin keratotic layer or subcutaneous fat layer by decreasing the diffusional resistance through reversible damage or increasing the solubility of the drugs in the skin in order to obtain enough skin-penetration for the drug to be effective. Additives performing these actions can be collectively referred to as permeation enhancers.

Generally, a polymer base is used for the transdermal delivery of drugs, as a solvent for the drugs and the skin permeation enhancers. A polymer base

should have sufficient mechanical strength, elasticity and adhesion to skin to be used as transdermal base. Much research has been undertaken to obtain these physical properties. For example, Okabe discloses a polymer base containing a water-soluble preparation, polyacrylamide gel. A gel including multivalent metal salt in polyacrylic acid or its salt [Japanese Patent Publication No. 3-167117], and gel including monomers having sulfonic acid groups [Japanese Patent Publication No. 4-91021] are also known. However, those water-soluble preparations are easily dissociated and since most of proteins have positive or negative charges at above or below their isoelectric point, there is a problem of the drug being bonded to the dissociated preparation.

Hydrogel patches for transdermal delivery of drugs are also known in the art. These patches typically include an inert, impervious backing layer, an adhesive layer containing a polymer base and the drug, optional selected excipients, and a release liner that is peeled off and discarded before applying the patch to the skin. Suitable polymer bases may be one or more members selected from the group consisting of polyvinyl alcohol and polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer, gelatin, alginate, hydroxyethyl methacrylate, cargeenane, hydroxyethyl cellulose, silicone rubber, agar, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, carboxyvinyl copolymer, polyethylene oxide, polyethylene glycol, polyacryl amide, polyhydroxyethyl methacrylate, polydioxolane, polyacrylic acid, polyacryl acetate, polyacryl amide and polyvinyl chloride may be used. Preferred are polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer and hydroxyethyl cellulose. The drug and selected excipients, if any, are directly incorporated into the hydrophilic polymer solution and then mixed to give a hydrogel composition containing the drug and excipients. See, for example, Makoto Haga et al., *Lecture Summary of the 112th Conference of The Pharmaceutical Society of Japan*, 4, 52(1992)], Riviere J. E. et al., *J. Pharm. Sci.*, **81(6)**, 504(1992), Banga A. K. et al., *Pharm. Res.*, **10(5)**, 697(1993), Japanese Patent Publication No. 3-193057. However, these

gels exhibit poor adhesion to skin.

Japanese Patent Publication No. 5-230313 discloses a gel obtained by mixing highly water-absorptive or hydrophilic polymer with polyvinyl alcohol. Though this gel has sufficient adhesion, it has poor mechanical strength and thus it is difficult to form the gel. There have been attempts to increase the crosslinking density by adding a crosslinking agent, like glutaldehyde, or by irradiation in order to increase the mechanical strength. Although this method improves the mechanical strength to some degree, the water content and adhesiveness of the gel decrease so that it is no longer suitable to be used as transdermal polymer base.

US Patent No. 4,593,053 discloses a hydrophilic gel matrix comprising a polar plasticizer and a hydrophilic gel matrix of polyvinyl pyrrolidone and polyvinyl alcohol. US Patent No. 5,082,663 discloses a water-soluble polymer gel of carboxymethyl cellulose including moisturizers like glycerol, sorbitol, propylene glycol and 1,3-butanediol. However, since these polymer gel matrices are water-soluble or hydrophilic, the permeation enhancers and the drugs used are limited to those that are water-soluble or hydrophilic. Since the skin layer like the keratotic layer or the subcutaneous fat, which functions as the greatest penetration barrier for most of drugs, is lipophilic or sub-lipophilic, it is well known that a sufficient penetration rate cannot be obtained with hydrophilic or water-soluble permeation enhancer only. In addition, most of conventional hydrogel compostions suffer the drawback of being unstable with respect to the water and humectant included therein. In other words, these preparations tend to synerese, i.e. to exclude the liquid, water component of the gel.

Accordingly, a technique of preparing an uniform, stable, hydrogel composition for transdermal drug delivery, which includes both a hydrophilic component, i.e. a hydrophilic polymer base, and lipophilic substances, i.e. permeation enhancers, is needed.

SUMMARY OF THE INVENTION

The present invention provides a stable hydrophilic polymer preparation which includes both hydrophilic and lipophilic substances as permeation enhancers in order to effectively deliver drugs transdermally. Briefly, in one aspect, the invention relates to an improved transdermal drug delivery composition comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an acrylate polymer which compatibilizes the lipophilic component, i.e. the enhancer, with the hydrophilic polymer base and which renders a uniform composition which is thermodynamically stable. The hydrophilic polymer base affects the mechanical strength, elasticity and adhesive properties and can be one or more hydrophilic polymers selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer, gelatin, alginate, hydroxyethyl methacrylate, carrageenan, hydroxyethyl cellulose, silicone rubber, agar, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, carboxyvinyl copolymer, polyethylene oxide, polyethylene glycol, polyacryl amide, polyhydroxyethyl methacrylate, polydioxolane, polyacrylic acid, polyacryl acetate, polyacryl amide and polyvinyl chloride. The acrylate polymer used as the compatibilizer can be a polymer of alkyl acrylate, alkyl methacrylate, acrylic acid, methacrylic acid or acrylate, or a copolymer thereof. The more preferable acrylate polymer is a copolymer comprising a 1:2 ratio of methyl methacrylate and ethyl acrylate or a copolymer comprising a 1:1 ratio of methacrylic acid and ethyl acrylate. The content of the acrylate polymer used as the compatibilizer in the present invention is within the range of 0.1-10wt.%, and is preferably 2-8wt.%, of the entire composition.

The present invention also provides methods of preparing an improved stable hydrogel composition for transdermal drug delivery which contains both a hydrophilic polymer base and lipophilic penetration enhancers. Also provided is a method to compatibilize a hydrophilic polymer base and lipophilic components in order to make a drug delivery preparation that is uniform and stable, thus overcoming the problems exhibited by current

preparations.

Brief Description of the Drawings

FIG. 1 is a schematic diagram of a matrix-type transdermal patch according to the present invention. <Notation of Drawings>

1: Impenetrable base

2: Polymer base including effective drug and permeation enhancer

3: Protection film to be removed before use

FIG. 2 represents the time-course accumulated penetration of buprenorphine hydrochloric acid salt penetrating the skin of a hairless mouse from a hydrogel matrix containing a lipophilic permeation enhancer and from a hydrogel matrix not containing a lipophilic permeation enhancer.

FIG. 3 represents the time-course of the weight change of a matrix caused by leaching of the lipophilic component from a hydrogel matrix that includes an acrylate polymer and a hydrogel matrix that does not includes an acrylate polymer as the compatibilizer.

Detailed Description of the Invention

Before the present composition and method of use thereof for transdermal delivery of pharmaceutical agents are disclosed and described, it is to be understood that this invention is not limited to the particular configurations, process steps, and materials disclosed herein as such configurations, process steps, and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a composition for delivering "a drug" includes reference to two or more of such

drugs, reference to "an adhesive" includes reference to one or more of such adhesives, and reference to "a permeation enhancer" includes reference to two or more of such permeation enhancers.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used herein, "effective amount" means an amount of a drug or pharmacologically active agent that is nontoxic but sufficient to provide the desired local or systemic effect and performance at a reasonable benefit/risk ratio attending any medical treatment. An effective amount of a permeation enhancer as used herein means an amount selected so as to provide the desired increase in skin permeability and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

As used herein, "transdermal" refers to delivery of a drug through the skin or mucosa and thus includes transmucosal delivery. Similarly, "skin" is meant to include mucosa.

As used herein, "drug," "pharmaceutical agent," "pharmacologically active agent," or any other similar term means any chemical or biological material or compound suitable for transdermal administration by the methods previously known in the art and/or by the methods taught in the present invention that induces a desired biological or pharmacological effect, which can include but is not limited to (1) having a prophylactic effect on the organism and preventing an undesired biological effect such as preventing an infection, (2) alleviating a condition caused by a disease, for example, alleviating pain or inflammation caused as a result of disease, and/or (3) either alleviating, reducing, or completely eliminating the disease from the organism. The effect can be local, such as providing for a local anaesthetic effect, or it can be systemic. This invention is not drawn to novel drugs or new classes of active agents. Rather it is limited to the mode of delivery of agents or drugs that exist in the state of the art or that may later be established as active agents and that are suitable for delivery by the present invention. Such substances include broad classes of compounds normally delivered into the body,

including through body surfaces and membranes, including skin. In general, this includes but is not limited to: antiinfectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelminthics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiabetic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including potassium and calcium channel blockers, beta-blockers, alpha-blockers, and antiarrhythmics; antihypertensives; diuretics and antidiuretics; vasodilators including general coronary, peripheral, and cerebral; central nervous system stimulants; vasoconstrictors; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers. By the method of the present invention, ionized drugs can be delivered, as can drugs of either high or low molecular weight.

As used herein, "permeation enhancer," "penetration enhancer," "chemical enhancer," or similar terms refer to compounds and mixtures of compounds that enhance the flux of a drug across the skin. The flux can be increased by changing either the resistance (the diffusion coefficient) or the driving force (the gradient for diffusion).

Chemical enhancers are comprised of two primary categories of components, i.e., cell-envelope disordering compounds and solvents, or binary systems containing both cell-envelope disordering compounds and solvents. The latter are well known in the art, *e.g.* U.S. Patent Nos. 4,863,970 and 4,537,776, incorporated herein by reference.

Cell envelope disordering compounds are known in the art as being useful in topical pharmaceutical preparations. These compounds are thought to assist in skin penetration by disordering the lipid structure of the cell-envelopes of

cells in the stratum corneum. A comprehensive list of these compounds is described in European Patent Application 43,738, published June 13, 1982, which is incorporated herein by reference. Examples of cell envelope disordering compounds that can be used as enhancers, without limitation, include saturated and unsaturated fatty acids and their esters, alcohols, monoglycerides, acetates, diethanolamides, and N,N-dimethylamides such as oleic acid, propyl oleate, isopropyl myristate, glycerol monooleate, glycerol monolaurate, methyl laurate, lauryl alcohol, lauramide diethanolamide, and mixtures thereof. Saturated and unsaturated sorbitan esters, such as sorbitan monooleate and sorbitan monolaurate, can also be used. It is believed that any cell envelope disordering compound is useful for the purposes of this invention.

Suitable solvents include water; diols, such as propylene glycol and glycerol; mono-alcohols, such as ethanol, propanol, and higher alcohols; DMSO; dimethylformamide; N,N-dimethylacetamide; 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted-alkyl-azacycloalkyl-2-ones (azones) and the like.

The present invention is based on the discovery that a stable hydrogel composition can be formulated for transdermal delivery of drugs, wherein an acrylate polymer is used as a compatibilizer which compatibilizes the lipophilic component, i.e. the enhancer, with the hydrophilic polymer base and which renders a uniform composition which is thermodynamically stable.

One embodiment of the present invention is characterized by a transdermal hydrogel composition comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an acrylate polymer which compatibilizes the lipophilic component, i.e. the enhancer, with the hydrophilic polymer base and which renders a uniform composition which is thermodynamically stable.

In detail, the transdermal hydrogel composition of the present

invention comprises:

(1) a hydrophilic polymer base;

(2) an effective amount of a pharmacologically active drug ;

(3) a lipophilic permeation enhancer;

(4) an acrylate polymer elected from the group consisting of alkyl acrylate, alkyl methacrylate, acrylic acid, methacrylic acid or copolymer thereof, which functions as a compatibilizer to enable said lipophilic permeation enhancer to be contained homogeneously and stably in said hydrophilic polymer base; and

(5) water as a solvent.

The hydrophilic polymer base affects the mechanical strength, elasticity and adhesiveness of the transdermal drug delivery system. Suitable hydrophilic polymers of the present invention can be one or more members selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer, gelatin, alginate, hydroxyethyl methacrylate, cargeenane, hydroxyethyl cellulose, silicone rubber, agar, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, carboxyvinyl copolymer, polyethylene oxide, polyethylene glycol, polyacryl amide, polyhydroxyethyl methacrylate, polydiorganosiloxane, polyacrylic acid, polyacryl acetate, polyacryl amide and polyvinyl chloride. Preferred hydrophilic polymers are selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer and hydroxyethyl cellulose.

The adhesiveness to the skin of the hydrophilic polymer base may be controlled through the selection of said polymers. The adhesive property means viscoelasticity which maintains semipermanent adhesion to most of the bases even under very low pressure. The hydrophilic polymer base in the present invention may have enough adhesiveness property by itself or it may function as a pressure sensitive adhesive, or be combined with additional adhesives, plasticizers or other additives.

It is particularly preferred, in terms of adhesion, to use a mixture of polyvinyl alcohol and polyvinyl pyrrolidone as the hydrophilic polymer base, in the range of 2-30wt.% of polyvinyl alcohol and 2-20wt.% of polyvinyl pyrrolidone based on the weight of the transdermal hydrogel composition, and more preferably in the range of 6-15wt.% of polyvinyl alcohol and 4-15wt.% of polyvinyl pyrrolidone.

When the polyvinyl alcohol content is too low, physical properties like the mechanical strength of the matrix worsen. However, if the polyvinyl alcohol content is too high, it is difficult to contain in the matrix the desired amount of drug, enhancer and other fillers due to an increase of solid particles in the base. Furthermore, the flexibility or adhesiveness of the matrix also worsens. When the polyvinyl pyrrolidone content is too low, the adhesiveness of the matrix worsens and the solubility of drugs in the composition decreases because the polymer functions as auxiliary solvent to the drug. If the polyvinyl pyrrolidone content is too high, the manufacturing process becomes difficult due to an increase in viscosity and decrease in the relative content of fillers like permeation enhancers.

Maleic anhydride/vinyl ether copolymer and/or hydroxyethyl cellulose may be used additionally in the mixture of polyvinyl alcohol and polyvinyl pyrrolidone. Preferably, 0.1-15wt.%, more preferably 3-10wt.%, of hydroxyethyl cellulose and/or 0.1-20wt.%, more preferably 0.2-10wt.%, of maleic anhydride/vinyl ether copolymer, are used additionally. Hydroxyethyl cellulose is known to increase the cohesion of the base and to have an effect of decreasing of skin irritation. However, if the hydroxyethyl cellulose content is high, the manufacturing process becomes difficult due to an increase in viscosity and decrease in the relative content of fillers like permeation enhancers. Maleic anhydride/vinyl ether copolymer even in small amount can improve physical properties like adhesion and mechanical strength of the matrix. However, excessive maleic anhydride/vinyl may increase the viscosity or delay the release of the drug.

The permeation enhancer of the present invention functions by various

mechanisms, such as by increasing the solubility and diffusion of the drug, changing the water-keeping capacity of the keratotic layer, softening the skin, increasing skin permeability, changing the interfacial state of the skin, or functioning as a hair follicle opener. The permeation enhancer of the present invention may work by more than one mechanism but its fundamental function is to increase permeability of the drug through the skin.

For the permeation enhancer, biphilic or lipophilic permeation enhancers, such as hydrophilic permeation enhancers like C_3-C_4 diols or C_2-C_3 alcohols, C_8-C_{18} saturated or unsaturated fatty acids, C_8-C_{18} saturated or unsaturated fatty alcohols, C_2-C_4 alkane diols, C_8-C_{18} fatty acid esters, fatty alcohol ethers, C_8-C_{18} saturated or unsaturated fatty acids, esters of C_1-C_4 alcohol or terpene compounds, may be used at less than 65wt.% of the total composition.

Examples of permeation enhancers are polyalcohols like propylene glycol, dipropylene glycol and polyethylene glycol, oils like olive oil, squalene and lanolin, fatty alcohol ethers like cetyl ether and oleyl ether, polyethylene glycol ether which increases the solubility of a drug, fatty acid esters like isopropyl myristate or fatty alcohols like oleyl alcohol that increase the diffusion of a drug, urea or urea derivatives like allantoin that affect the water-keeping capacity of the keratin in skin tissue, polar solvents like dimethyl decyl phosphoxide, methyl octyl sulfoxide, dimethyl lauryl amide, dodecyl pyrrolidone, isosorbitol, dimethyl acetonide, dimethyl sulfoxide, decyl methyl sulfoxide and dimethyl formamide that affect the penetration properties of keratin, keratin softeners like salicylic acid, penetration adjuvants like amino acids, hair follicle openers like benzyl nicotinate and high-molecular fatty acid surfactants like lauryl sulfate which change the status of administered drug and skin surface.

In particular, auxiliary solvents may be added to drugs and drug polymers which are hardly soluble in a hydrophilic system. In the present invention, auxiliary solvents like lecithin, retinal derivatives, tocopherol, dipropylene glycol, triacetin, propylene glycol, saturated or unsaturated fatty

acid, mineral oil, silicone fluid and butylbenzyl phthalate may be used.

For another functioning agents, oleic acid, linoleic acid, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopheryl acetated, tocopheryl linolate, propyl oleate, isopropyl palmitate, oleamide and polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether and polyoxyethylene (10) oleyl ether and polysorbate 20 marketed by ICI America s trade mark Brij™ 30, 93, 97 and Tween™ 20 may be used additionally.

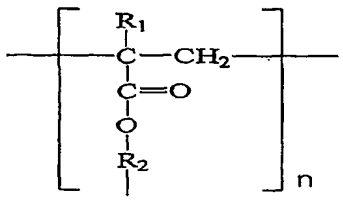
Though the mechanisms of said permeation enhancer, auxiliary solvent and other functioning agents are different, they may be classified as permeation enhancers because they facilitate skin penetration of drugs through the skin. These permeation enhancers can be classified as hydrophilic, lipophilic or biphilic according to their properties. Most of the permeation enhancers, except for hydrophilic skin-penetration facilitators with hydrophilic groups and few carbon atoms like C_3-C_4 diols or C_2-C_3 alcohols, may be classified as lipophilic or biphilic. Specific examples of permeation enhancers are hydrophilic compounds selected from propylene glycol, glycerol, ethanol, isopropyl alcohol, dimethylsulfoxide and *n*-methyl pyrrolidone; and one or more lipophilic compounds selected from the group consisting of lauryl alcohol, propylene glycol monolaurate, lauroglycol, isopropyl myristate, triacetin, nonanol, oleyl alcohol, linoleyl alcohol, methyl laurate, glycerol monolaurate and glycerol monooleate.

Permeation enhancerd to be used in the present invention includes said known compounds, and its specific examples and more details are described in *Pharm. Tech.*, 1990 Sept., 132-136; *Pharm. Tech.*, 1990 Oct., 54-60; *Pharm. Tech.*, 1993 March, 72-98; *Pharm. Tech.*, 1993 Apr., 62-90; and *Pharm. Tech.*, 1993 May, 68-76.

In the polymer hydrogel composition of the present invention, other functioning agents known to facilitate transdermal delivery of drugs may additionally be included.

In the present invention, compatibilizers like alkyl acrylate, alkyl methacrylate, acrylic acid, methacrylic acid or acrylate copolymer thereof,

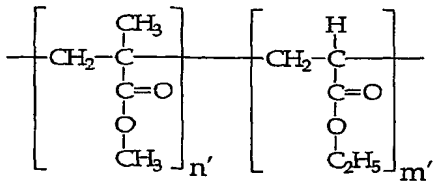
preferably having average molecular weight within the range of 50KD to 5000 KD, more preferably 100KD to 1000 KD, are used to compatibilize the hydrophobic or lipophilic permeation enhancers in the hydrophilic base composition. It is preferable to use an acrylate polymer expressed by the following Formula (1),



(1)

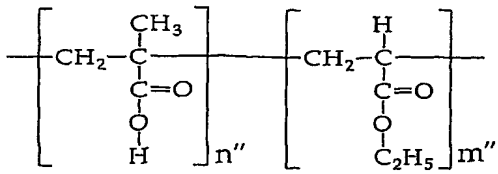
wherein R_1 and R_2 may be identical or different and represent a hydrogen atom or C_1-C_8 alkyl; and n represents the number of repeated units (inside the bracket) and is an integer between 500 to 50,000. In said acrylate polymer expressed by Formula (1), R_1 is preferred to be a hydrogen atom or methyl group; and R_2 a methyl or ethyl group.

The more preferable copolymer comprising a 1:2 ratio of methyl methacrylate and ethyl acrylate expressed by the following Formula (1a) or a copolymer comprising a 1:1 ratio of methacrylic acid and ethyl acrylate expressed by the following Formula (1b),



(1a)

wherein the ratio of n':m' is 1:2, n' is an integer between 200 to 10,000 and m' is an integer between 400 to 20,000.



(1b)

wherein the ratio of n":m" is 1:1, and n" and m" is an integer between 300 to 10,000.

For the compound expressed by Formula (1a), polymethacrylate compounds marketed as Eudragit™ series by Rohm Pharma (Germany) were used; and for the compound expressed by Formula (1b), polymethacrylate compounds marketed as Kollicoat™ series by BASF (USA) were used, in the Examples of the present invention.

The acrylate polymer used as the compatibilizer in the present invention 0.1-10wt.%, preferably 2-8wt.%, of the entire transdermal hydrogel composition. If the compatibilizer content included in the transdermal hydrogel composition is too low, the lipophilic component may be syneresed due to poor compatibility; otherwise if the content is too high, physical properties like the mechanical strength of the matrix may worsen.

The effective drug contained in the transdermal hydrogel composition according to the present invention is pharmacologically or physiologically active for treatment or prevention, and provides a targeted effect when delivered to the body. More specifically, any drug that induces a local or general pharmacological effect for treatment, diagnosis or prevention in plants or animals is regarded to belong to the scope of the present invention. Bioactive drugs like insecticide, pesticides, sunscreens and cosmetics are included in the effective drug list of the present invention. The effective drug is used solely or may be mixed with another effective drug for the prevention, treatment, diagnosis or remedy of diseases or syndromes.

The effective drug is used in a pharmacologically effective amount. This amount means the concentration of a drug that enables a targeted amount of the drug to penetrate the skin with a zero-order penetration rate during the administration period of the drug. This concentration is determined by many parameters including the kind of drug, the administration period of each unit, flow rate of the drug in the system and others. The required amount of

effective drug may be determined empirically from the flow rate of the drug and the permeation enhancer used to penetrate the skin. If the required flow rate is determined, a transdermal administration system is designed to have at least the same release rate with the required flow rate. Of course, the surface area of the transdermal administration system affects the release of the drug from the system. The skin-penetration rate means the rate of drug penetrating the skin. This rate may or may not be affected by the release rate of drug from the carrier, as is known in the field of the related art.

The effective drug and mixtures thereof in the present invention can be provided in various forms for optimal drug delivery. Accordingly, the drug may exist as a free-base, acid, salt, ester, or other pharmacologically available derivative forms or molecular complexes.

Various thickeners, fillers or other additives known to be useful for the transdermal drug delivery system may be added to the transdermal hydrogel composition according to the present invention. For example, addition of materials like clay that absorbs water into the composition, is known to increase the adhesive properties without reducing the drug delivery rate. Examples of the clay are kaolinites like vaolinite, anarchsite, dickite and nacrite, montomorillonites like montmorillonite, bentonite, verdelite and montronite, illites/muscobites like illite and glauconite, chlorites and polygorsites like attapulgite, halloysite, metaboloysite, allophane and aluminum silicate clay.

Also, antiseptics can be included in the composition of the present invention. Examples of antiseptic are sodium azide, aminoethyl sulfonic acid, benzoic acid, sodium benzoate, sodium edetate, cetylpyridinum chloride, benzalkonium chloride, benzetonium chloride, sodium sulfate anhydride, isobutyl *p*-oxybenzoate, isopropyl *p*-oxybenzoate and methyl *p*-oxybenzoate.

The transdermal hydrogel base composition of the present invention can be used as the adhesive part of any transdermal delivery system or in a matrix type apparatus comprising an adhesive monolayer. FIG. 1 is a typical schematic diagram of a matrix type transdermal administration apparatus

comprising an impenetrable base 1, a polymer base 2 including the drug and enhancer, and a protection film 3 to be removed before use. The hydrogel base composition of the present invention can be used as the polymer base 2. Also, the hydrogel base composition of the present invention may be used by adhering it to a common auxiliary base, such as an impenetrable support 1. For the common auxiliary base, a plastic sheet like polyethylene, polypropylene, an ethylene/vinyl acetate copolymer, vinylon, polyester, polyurethane and nylon, a nonwoven fabric like rayon and polyester, a woven fabric like acryl, silk or cotton and a composite layer of these supports may be used.

Hereunder is given a more detailed description of the present invention using examples and comparative examples. However, it should not be construed as limiting the scope of the present invention.

Comparative Examples 1 & 2

In Comparative Example 1, a transdermal drug delivery matrix including a hydrophobic permeation enhancer was prepared as follows. In a suitable container, a predetermined amount of buprenorphine hydrochloric acid salt, propylene glycol, triacetin, ethanol, lauryl alcohol, glycerol and pure water were added and stirred until the mixture became completely uniform. A predetermined amount of hydroxyethyl cellulose (number-average molecular weight (M_n): 250,000), and polyvinyl pyrrolidone was then added, dissolved uniformly then followed by addition of a polyvinyl alcohol (degree of polymerization: 500-2,000) aqueous solution and then mixed uniformly, the mixture was then cooled for about 10hr in a 4-10°C refrigerator.

In Comparative Example 2, a matrix not containing a hydrophobic permeation enhancer was prepared the same way as described in Comparative Example 1 except that no triacetin or lauryl alcohol was added. The composition of Comparative Examples 1 & 2 is shown in Table 1.

Table 1

Composition	Content (wt%)	
	Comparative Example 1	Comparative Example 2
Buprenorphine Hydrochloric Acid Salt	2.0	2.0
Propylene Glycol	19.0	24.0
Triacetin (Glycerol Triacetate)	8.5	-
Ethanol	14.0	12.0
Lauryl Alcohol	0.5	-
Glycerol	4.0	4.0
Pure Water	14.0	20.0
Hydroxyethyl Cellulose (M_n: 250,000)	4.0	4.0
Polyvinyl Pyrrolidine (Collidon 90*)	10.0	10.0
25% Polyvinyl Alcohol Solution (degree of polymerization: 500-2,000)	24.0	24.0
Total	100.0	100

The skin-penetration test of the drug for the matrices prepared from Comparative Examples 1 & 2 were performed as follows. The receptor phase of a Franz Cell was filled with pure water and maintained at 32±0.5°C . The back skin of a male hairless mouse was removed and stabilized for 1hr before the experiment. After cutting the prepared matrix according to the donor cell size, 300μL of sample was taken from the cell after 2, 4, 8, 18, 24, 48 and 72hr, and quantitative analysis was performed using liquid chromatography. The results are shown in FIG. 2 and Table 2.

Table 2

Items	Comparative Example 1	Comparative Example 2
Drug Penetration Rate (Flux; μg/cm²/hr)	18.49	1.76
Retardation Time (hr)	1.19	0.50

In Comparative Example 1 wherein a lipophilic permeation enhancer was used, the skin-penetration rate was about 10 times higher than that of Comparative Example 2. Though the retardation time of Comparative Example 2 appeared to be short, the retardation time itself was not of great significance because the penetration rate, and hence the penetration amount, was not as great as is shown in FIG. 2. However, the hydrophobic permeation enhancer (triacetin and lauryl alcohol) used in Comparative Example 1 was syneresed with time due to the low compatibility between the lipophilic component and the hydrophilic base.

The composition of the present invention overcomes this problem and is illustrated by the following examples.

Example 1

After adding a predetermined amount of buprenorphine hydrochloric acid salt in a suitable container, a predetermined amount of propylene glycol, triacetin, ethanol, lauryl alcohol, glycerol, BASF's Kollicoat MAE 30D™ as acrylate compatibilizer and pure water were added and stirred until the mixture became completely uniform. After adding a predetermined amount of hydroxyethyl cellulose (M_n: 250,000) and polyvinyl pyrrolidone herein and dissolving them uniformly, a predetermined amount of a polyvinyl alcohol (degree of polymerization: 500-2,000) aqueous solution was added, mixed uniformly, and then cooled for about 10hr in a 4-10°C refrigerator. The composition of Example 1 is shown in the following Table 3.

Table 3

Composition	Content (wt.%)
Buprenorphine Hydrochloric Acid Salt	2.0
Propylene Glycol	19.0
Triacetin (Glycerol Triacetate)	8.5
Ethanol	14.0
Lauryl Alcohol	0.5
Glycerol	4.0
Kollicoat MAE 30D™	8.3
Pure Water	5.7
Hydroxyethyl Cellulose (M_n: 250,000)	4.0
Polyvinyl Pyrrolidine (Collidon 90™)	10.0
25% Polyvinyl Alcohol Solution (degree of polymerization: 500-2,000)	24.0
Total	100.0

In order to identify the increase of compatibility due to the acrylate polymer included in the present invention, the matrices obtained from Example 1 and Comparative Example 1 were sealed with aluminum foil and kept at room temperature. The syneresed liquid portion was removed with Kim Wipes after 0, 1, 2, 4, 8, 16, 24, 48, 72 and 96hr. The weight of the matrices was measured and their change from the initial weight was calculated in %. The results are shown in FIG. 3 and the following Table 4.

Table 4

Time (hr)	Change of Matrix Weight (%, Mean ± S.D.)	
	Comparative Example 1	Example 1
1	96.4± 0.84	99.0± 0.34
2	95.6± .089	99.7± 0.21
4	94.8± 0.21	98.3± 0.74
8	93.2± 0.16	99.3± 0.52
16	92.0± 0.96	99.0± 0.14
24	90.8± 0.91	98.3± 0.38
48	90.4± 0.38	98.0± 0.78
72	90.0± 0.27	97.7± 0.34
96	90.0± 0.41	98.0± 0.24

The weight change of the matrices prepared as in Comparative Example 1 was severe due to syneresation of the thermodynamically unstable composition wherein the lipophilic components were poorly compatible with the hydrophilic polymer base. In addition, volatilization of a volatile solvent like ethanol also contributed to weight loss in some degree. However, in Example 1 wherein an acrylate compatibilizer was used, there was little weight change due to phase separation even after 96hr at room temperature. Therefore, the hydrogel composition of the present invention exhibits superior compatibility and stability of the lipophilic penetration enhancer contained in a hydrophilic polymer base.

Examples 2-14 were performed while adjusting the composition contents of the drug, the hydrogel polymer base and the lipophilic permeation enhancer.

Example 2

Composition	Content (wt.%)
Estradiol	1.0
Propylene Glycol	30.0
Polypropylene Glycol Monolaurate	7.0
Ethanol	14.0
Cremophore RH 40™	0.8
Eudragit NE 30D™	6.7
Pure Water	15.3
Polyvinyl Pyrrolidine (Collidon 30™)	4.0
Maleic anhydride/Vinyl Ether Copolymer (Gantrez AN 169™)	21.2
Total	100.0

Example 3

Composition	Content (wt.%)
Progesterone	1.0
Propylene Glycol	27.0
Lauroglycol (Lacroglyceryl FCC™)	7.0
Ethanol	15.0
Cremophore RH 40™	6.0
Eudragit NE 30D™	6.7
Pure Water	15.3
Polyvinyl Pyrrolidine (Collidon 30™)	4.0
Maleic Anhydride Copolymer (Gantrez AN 169™)	18.0
Total	100.0

Example 4

Composition	Content (wt.%)
Albuterol	2.0
Propylene Glycol	20.0
Isopropyl Myristate	6.0
Isopropyl Alcohol	12.0
Cremophore RH 40™	15.0
Eudragit NE 30D™	11.7
Pure Water	11.8
Polyvinyl Pyrrolidine (Collidon 90™)	4.0
Maleic Anhydride Copolymer (Gantrez AN 169™)	17.5
Total	100.0

Example 5

Composition	Content (wt.%)
Nitroglycerin	3.0
Propylene Glycol	15.0
Triacetin (Glycerol Triacetate)	10.0
Ethanol	14.0
Lauryl Alcohol	3.5
Lactic Acid	2.0
Kollicoat MAE 30D™	18.3
Pure Water	7.2
Polyvinyl Pyrrolidine (Collidon 90™)	4.0
Maleic Anhydride Copolymer (Gantrez AN 169™)	23.0
Total	100.0

Example 6

Composition	Content (wt.%)
Captopril	2.0
Propylene Glycol	12.0
Triacetin (Glycerol Triacetate)	7.0
Ethanol	8.0
Lauryl Alcohol	2.5
Lactic Acid	2.0
Kollicoat MAE 30D™	11.7
Pure Water	12.8
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	32.0
Maleic Anhydride Copolymer (Gantrez AN 169™)	10.0
Total	100.0

Example 7

Composition	Content (wt.%)
Pilocarpine	2.0
Propylene Glycol	19.0
Triacetin (Glycerol Triacetate)	9.0
Ethanol	14.0
Lauryl Alcohol	0.7
Eudragit NE 30D™	11.7
Pure Water	6.6
Hydroxyethyl Cellulose (M_n: 250,000)	4.0
Polyvinyl Pyrrolidine (Collidon 90™)	8.0
20% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	25.0
Total	100.0

Example 8

Composition	Content (wt.%)
Diazepam	2.0
Propylene Glycol	11.0
Triacetin (Glycerol Triacetate)	5.5
Ethanol	17.5
Lauryl Alcohol	0.6
Nonanol (Nonyl Alcohol)	0.6
Eudragit NE 30D™	9.3
Pure Water	14.0
Hydroxyethyl Cellulose (M_n: 250,000)	4.5
Polyvinyl Pyrrolidine (Collidon 90™)	11.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	24.0
Total	100.0

Example 9

Composition	Content (wt.%)
Chlorpromazine	2.0
Propylene Glycol	11.0
Triacetin (Glycerol Triacetate)	4.5
Ethanol	17.5
Propylene Glycol Monolaurate	2.0
Nonanol (Nonyl Alcohol)	0.6
Eudragit NE 30D™	8.0
Pure Water	14.9
Hydroxyethyl Cellulose (M_n: 250,000)	4.5
Polyvinyl Pyrrolidine (Collidon 90™)	11.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	24.0
Total	100.0

Example 10

Composition	Content (wt.%)
Lidocaine	2.0
Propylene Glycol	19.5
Triacetin (Glycerol Triacetate)	5.0
Ethanol	14.0
Lauryl Alcohol	0.7
Eudragit NE 30D™	12.7
Pure Water	6.1
Hydroxyethyl Cellulose (M_n: 250,000)	5.0
Polyvinyl Pyrrolidine (Collidon 90™)	11.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	20.0
Total	100.0

Example 11

Composition	Content (wt%)
Buprenorphine	2.0
Propylene Glycol	19.5
Triacetin (Glycerol Triacetate)	9.0
Ethanol	14.0
Lauryl Alcohol	0.7
Glycerol	2.0
Eudragit NE 30D™	12.7
Pure Water	12.1
Hydroxyethyl Cellulose (M_n: 250,000)	5.0
Polyvinyl Pyrrolidine (Collidon 90™)	11.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	12.0
Maleic Anhydride Copolymer (Gantrez AN 169™)	2.0
Total	100.0

Example 12

Composition	Content (wt.%)
Buprenorphine Hydrochloric Acid Salt	2.0
Propylene Glycol	19.5
Triacetin (Glycerol Triacetate)	9.0
Ethanol	14.0
Lauryl Alcohol	0.7
Glycerol	2.0
Eudragit NE 30D™	12.7
Pure Water	12.1
Hydroxyethyl Cellulose (M_n: 250,000)	5.0
Polyvinyl Pyrrolidine (Collidon 90™)	11.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	12.0
Total	100.0

Example 13

Composition	Content (wt%)
Nicotine	14.0
Propylene Glycol	10.0
Triacetin (Glycerol Triacetate)	4.0
Ethanol	15.6
Lauryl Alcohol	1.2
Nonanol (Nonyl Alcohol)	1.2
Eudragit NE 30D™	6.7
Pure Water	15.3
Hydroxyethyl Cellulose (M_n: 250,000)	4.0
Polyvinyl Pyrrolidine (Collidon 90™)	8.0
25% Polyvinyl Alcohol Aqueous Solution (Degree of Polymerization: 500-2,000)	20.0
Total	100.0

Example 14

Composition	Content (wt%)
Prostaglandin-E1	2.0
Propylene Glycol	17.0
Triacetin (Glycerol Triacetate)	8.5
Ethanol	12.0
Lauryl Alcohol	0.5
Glycerol	4.0
Kollicoat MAE 30D™	13.3
Pure Water	4.7
Hydroxyethyl Cellulose (M_n: 250,000)	4.0
Polyvinyl Pyrrolidine (Collidon 90™)	10.0
25% Polyvinyl Alcohol Solution (degree of polymerization: 500-2,000)	24.0
Total	100

As explained above, the transdermal hydrogel composition according to the present invention contains an acrylate polymer as a compatibilizer such that a hydrophilic polymer base and a lipophilic permeation enhancer can be applied simultaneously in order to facilitate the effective local or general skin-penetration of the pharmacologically active drug.

The above description and examples are intended to be illustrative and not limiting of the present invention. One skilled in the art will appreciate that there may be many variations and alternatives suggested by the above invention. These variations and alternatives are intended to be within the scope of this invention as set forth in the following claims.

CLAIMS

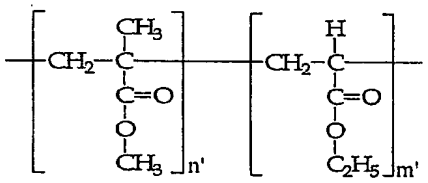
What is claimed is:

1. A transdermal drug delivery composition comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an acrylate polymer which compatibilizes said lipophilic enhancer with said hydrophilic polymer base and which renders said composition thermodynamically stable.

2. The composition according to claim 1, wherein said acrylate polymer is within the range of 0.1-10wt.% based on the entire composition.

3. The composition according to claim 2, wherein said acrylate polymer is included in the range of 2-8wt.% to the entire composition.

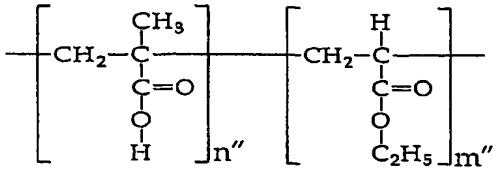
4. The composition according to claim 1, wherein said acrylate polymer is a copolymer comprising a 1:2 ratio of methyl methacrylate and ethyl acrylate expressed by the following Formula (1a),



(1a)

wherein the ratio of n′ to m′ is 1:2, n′ is an integer between 200 to 10,000 and m′ is an integer between 400 to 20,000.

5. The composition according to claim 1, wherein said acrylate polymer is a copolymer comprising a 1:1 ratio of methacrylic acid and ethyl acrylate expressed by the following Formula (1b),



(1b)

wherein the ratio of n" to m" is 1:1 and n" and m" is an integer between 300 to 10,000.

6. The composition according to claim 1, wherein said acrylate polymer has average molecular weight in the range of 50KD to 5000KD.

7. The composition according to claim 1, wherein said effective drug is one or more compounds selected from the group consisting of beta-adrenaline activators, beta-adrenaline inhibitors, analgesics, antianginas, antiarrhythmic drugs, antidepressants, antiestrogens, antigonadotrophins, hypotensive drugs, anti-inflammatory drugs, anti-tumor drugs, anti-prostatomegaly drugs, antipsychotics, spasmolytics, antianxiety drugs, bronchodilators, calcium regulators, cardiotonics, dopamine receptors, liver enzyme inducers, estrogens, glucocorticoids, mineral corticoids, monoamine oxidase inhibitors, muscle relaxation drugs, narcotic antagonists, progestogens and peripheral vasodilators.

8. The composition according to claim 7, wherein said effective drug is one or more analgesics selected from the group consisting of buprenorphine and fentanyls like fentanyl, norfentanyl, sufentanyl and alfentanyl.

9. The composition according to claim 1, wherein said hydrophilic polymer is one or more compounds selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer, gelatin, alginate, hydroxyethyl methacrylate, cargeenane, hydroxyethyl cellulose, silicone rubber, agar, hydroxypropyl cellulose, hydroxypropyl

methyl cellulose, methyl cellulose, carboxyvinyl copolymer, polyethylene oxide, polyethylene glycol, polyacryl amide, polyhydroxyethyl methacrylate, polydioxolane, polyacrylic acid, polyacryl acetate, polyacryl amide and polyvinyl chloride.

10. The composition according to claim 9, wherein said hydrophilic polymer is one or more compounds selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, maleic anhydride/vinyl ether copolymer and hydroxyethyl cellulose.

11. The composition according to claim 10, comprising 2-30wt.% of polyvinyl alcohol and 2-20wt.% of polyvinyl pyrrolidone based on said hydrophilic polymer.

12. The composition according to claim 11, wherein said hydrophilic polymer further comprises 0.1-15wt.% of hydroxyethyl cellulose or 0.1-20wt.% of maleic anhydride/vinyl ether copolymer.

13. The composition according to claim 1, wherein said permeation enhancer is one or more compounds selected from the group consisting lauryl alcohol, propylene glycol monolaurate, lauroglycol, isopropyl myristate, triacetin, nonanol, oleyl alcohol, linoleyl alcohol, methyl laurate, glycerol monolaurate and glycerol monooleate.

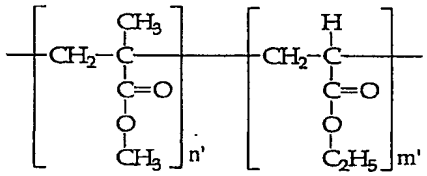
14. The composition according to claim 13, wherein said permeation enhancer is included in the range of 0.1-65wt.% to the entire composition.

15. A transdermal drug delivery composition comprising a hydrophilic polymer base comprising 2-30wt.% of polyvinyl alcohol and 2-20wt.% of polyvinyl pyrrolidone of said hydrophilic polymer base; a drug; a 0.1-65wt.% of a lipophilic permeation enhancer based on the entire composition; and

0.1-10wt.% of a compatibilizer based on the entire composition, said compatibilizer consisting essentially of an acrylate polymer which compatibilizes said lipophilic enhancer with said hydrophilic polymer base and which renders said composition thermodynamically stable.

16. The composition according to claim 15, wherein said acrylate polymer is included in the range of 2-8wt.% of the entire composition.

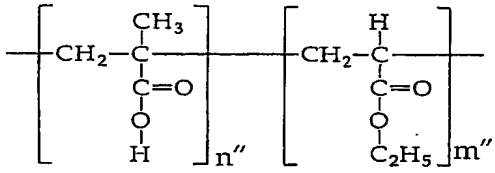
17. The composition according to claim 15, wherein said acrylate polymer is a copolymer comprising a 1:2 ratio of methyl methacrylate and ethyl acrylate expressed by the following Formula (1a),



(1a)

wherein the ratio of n' to m' is 1:2, n' is an integer between 200 to 10,000 and m' is an integer between 400 to 20,000.

18. The composition according to claim 15, wherein said acrylate polymer is a copolymer comprising a 1:1 ratio of methacrylic acid and ethyl acrylate expressed by the following Formula (1b),



(1b)

wherein the ratio of n" to m" is 1:1 and n" and m" is an integer between 300 to 10,000.

19. The composition according to claim 15, wherein said acrylate polymer has average molecular weight in the range of 50KD to 5000KD.

20. The composition according to claim 15, wherein said hydrophilic polymer further comprises 0.1-15wt.% of hydroxyethyl cellulose or 0.1-20wt.% of maleic anhydride/vinyl ether copolymer.

21. The composition according to claim 15, wherein said permeation enhancer is one or more compounds selected from the group consisting lauryl alcohol, propylene glycol monolaurate, lauroglycol, isopropyl myristate, triacetin, nonanol, oleyl alcohol, linoleyl alcohol, methyl laurate, glycerol monolaurate and glycerol monooleate.

22. A transdermal drug delivery system comprising the transdermal drug delivery composition according to one of the claims 1 to 21.

DRAWINGS

FIG. 1

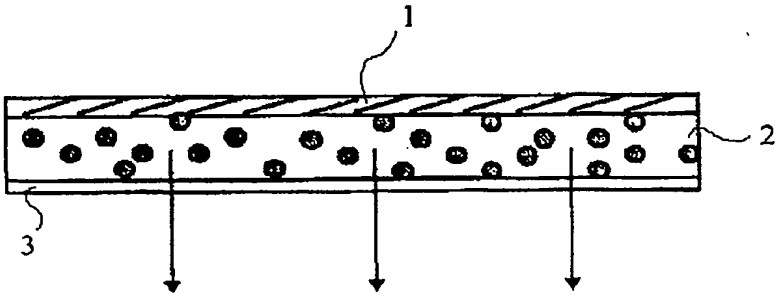


FIG. 2

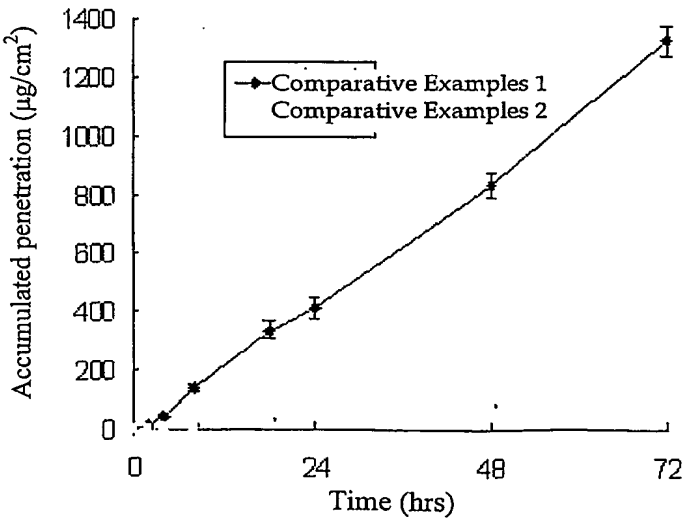
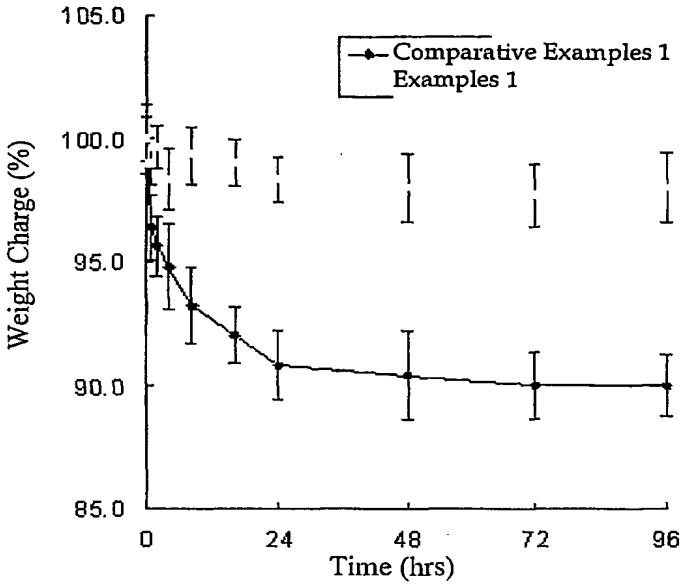


FIG. 3


105.0
100.0
95.0
90.0
85.0
Weight Charge (%)
0
24
48
72
96
Time (hrs)
Comparative Examples 1
Examples 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 01/00783

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 9/70, A61F 13/02, A61L 15/16, A61M 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K, A61F, A61L, A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/00058 A1 (NOVEN PHARMACEUTICALS, INC.) 7 January 1993 (07.01.93) *page 17, line 27 - page 18, line 28; page 25, line 22 - page 26, line 8; table II; claims.*	1-9,13,14
X	WO 99/15210 A2 (NOVEN PHARMACEUTICALS, INC.) 1 April 1999 (01.04.99) *page 8, line 4 - page 10, line 20; page 15, lines 24,30; page 58, line 4 - page 64, line 8, claims 1-3,5,15,16.*	1-10,13,14
X	EP 0904778 A1 (NITTO DENKO CORPORATION) 31 March 1999 (31.03.99) *abstract, page 4, lines 5-32 and 45; page 5, line 54 - page 6, line 8, claims 1-3.*	1,7,9,13
X	WO 95/18603 A1 (NOVEN PHARMACEUTICALS, INC.) 13 July 1995 (13.07.95) *page 12, line 16 - page 28, line 37; page 29, line 21 - page 30, line 30; table I; abstract; claims.*	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
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„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2001 (24.07.2001)	16 August 2001 (16.08.2001)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer KRENN Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int_____al application No.
PCT/KR 01/00783

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
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				NO	A	934523	10-02-1994
				NZ	A	243200	25-11-1993
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				US	BA	6235306	22-05-2001
				US	A	5656286	12-08-1997
				US	A	6024976	15-02-2000
				ZA	A	9209992	23-06-1994
				AT	E	99176	15-01-1994
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